

REMARKS

Status of the Claims

Claims 33 and 53-81 are currently pending. Claims 33, 53-57, 62, 64-66, 68, and 70-73, are withdrawn from consideration as being directed to a non-elected invention. Claims 1-32 and 34-52 have been canceled. Claims 74-81, directed to the same invention as claims 58-61, 63, 67, and 69, are newly added. Claims 58-61, 63, 67, 69, and 74-81 are currently under examination.

Amendments to the Claims

The amendments to claims 58-61 and 74 and addition of new claims 74-81 do not introduce prohibited new matter. Support for the amendments and the new claims can be found throughout the specification. Representative support for the amendments to claims 58-61 and 74 can be found in claim 1 as originally filed, wherein liposomes are excluded. Representative support for new claims 74-81 can be found in the table below.

Claim(s)	Representative Support
75	Claim 58; Paragraph 45, line 3; Example 4
76	Claim 59
77	Claim 60; Paragraph 47, lines 3-5; Example 2
78	Claim 61
79	Claim 63
80	Claim 67
81	Claim 69
82	Claim 74

Double Patenting

Claims 58-61, 63, 67, 69, and 74 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 51-59 of copending application 10/519,193 and claims 1-15 of copending application 11/018,574.

Applicants respectfully point out that the claims 58-61, 63, 67, 69, and 74, as they stand, are not directed to methods of preparing liposomal compositions. Thus, claims 58-61, 63, 67, 69, and 74 of the present application and the claims of the copending applications are not obvious over each other.

Moreover, Applicants respectfully point out that new claims 75-81 of the present application are directed to modifying an agent to enhance its efficacy of targeting to an activated vascular site and require associating an agent with a cationic component to produce a composition, dispersing the composition in a medium to form colloids, measuring the zeta potential of the composition comprising the colloids and, and selecting composition having a zeta potential of about +30 mV to +65 mV for targeting an activated vascular site. Applicants unexpectedly discovered that the optimal zeta potential for targeting a composition to an activated vascular site is about +30 mV to +65 mV. The copending applications do not include the step of optimizing the zeta potential of the composition to between about +30 mV to +65 mV. The copending applications also do not disclose preparing the composition for targeting an activated vascular site and do not require measuring the zeta potential of the composition and selecting composition having a zeta potential of between about +30 mV to +65 mV. Thus, the claims in the present application and the copending applications are not obvious over each other.

Rejections Under 35 U.S.C. § 102(e)

Claims 58, 59, 61, 63, 67, 69, and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 5,770,222 (“Unger”).

Claims 58 and 61 have been amended to exclude liposomes. Claims 59, 63, 67, 69, and 74 are dependent upon claim 58 or 61 and therefore include the features of these claims. In contrast to the claimed invention, Unger discloses liposomal preparations. Thus, Unger does not anticipate the claimed invention.

Moreover, new claims 75 and 78 are directed to a method of modifying an agent to enhance its efficacy of targeting an activated vascular site comprising associating the agent with one or more cationic components to produce a composition, dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm, measuring the zeta potential of the composition comprising the colloids, and selecting composition having a zeta

potential of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting an activated vascular site. The claims require that the size of the colloids in the composition to be between about 10 nm to about 400 nm. Moreover, Applicants unexpectedly discovered that about +30 mV to +65 mV is the optimal range of zeta potential for targeting an agent to an activated vascular site (figures 2 and 3). Thus, the claims of the present invention also require measuring the zeta potential of the composition comprising the dispersed colloids and selecting composition having a zeta potential of between about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting an activated vascular site. Also, claim 78 require that the cationic components comprise magnetosome.

Applicants respectfully submit that Unger does not teach a method of modifying an agent to enhance its efficacy for targeting an activated vascular site. Moreover, Unger does not disclose measuring the zeta potential of their liposomal composition and selecting for liposomal composition having a zeta potential of between about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5. Further, Unger only teaches methods of preparing cationic liposomal compositions having particles with a preferred mean diameter of between 30 nm to 5 μ m. This range of mean diameter is much broader than what is claimed by the present invention and only overlaps with the range claimed by the present invention from about 30 nm to about 400 nm. Moreover, the overlap in the two ranges is less than 10% of the range disclosed by Unger.

Furthermore, Applicants respectfully point out that when an agent is mixed with a cationic lipid to form a composition, the composition can have various zeta potentials depending on the zeta potential of the agent and cationic lipid to begin with, the amount of each component in the composition, and the solution in which the components are formed. Accordingly, Unger does not include all the steps recited by the claimed method, and the compositions prepared by the method of Unger do not have the specific range of zeta potential recited in the claims.

MPEP 2131.03(II) states that in order to anticipate the claims, the reference must disclose the claimed subject matter with “sufficient specificity” and cites *Atofina v. Great Lakes Chemical Corp* for describing “sufficient specificity” as to constitute anticipation of the claims. In *Atofina*, the court concluded that an earlier genus reference does not anticipate a narrow species, if the prior art reference does not describe the narrower claimed range with sufficient specificity. *Atofina v. Great Lakes*, 78 USPQ2d 1417 (Fed. Cir. 2006). The court held that a

prior art publication disclosing 100 °C to 500 °C for synthesizing difluoromethane does not anticipate a claimed method of synthesizing difluoromethane limited to the specific range of 330 °C to 450 °C, even though the prior art range is broader than and fully encompasses the claimed range. *Id.* at 1424. The court found that no reasonable fact finder could conclude that the prior art described the claimed range with sufficient specificity to anticipate the temperature range limitation recited in the claims. *Id.*

Similar to the fact situation in *Atofina*, Unger does not disclose a method of obtaining a liposomal composition having the recited particle size and zeta potential with sufficient specificity. Unger discloses obtaining a composition having particles with a diameter in the range of 30 nm to 5 µm which is much broader than between about 10 nm to about 400 nm, the size of the particles recited in the claims. Also, Unger does not disclose selecting compositions having the zeta potential of between about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting an activated vascular site. Thus, Unger does not teach the range of the particle size or zeta potential recited in the claims with sufficient specificity to anticipate the claims. Accordingly, Unger does not teach or anticipate the claimed invention.

B. Claims 58, 59, 63, 67, 69 and 74 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,110,490 (“Thierry”).

Claim 58 has been amended to exclude liposomes. Claims 59, 63, 67, 69, and 74 are dependent upon claim 58 and therefore include the features of claim 58. In contrast to the claimed invention, Thierry discloses liposomal preparations. Thus, Thierry does not anticipate the claimed invention.

Moreover, new claim 75 is directed to a method of modifying an agent to enhance its efficacy of targeting an activated vascular site comprising associating the agent with one or more cationic components to produce a composition, dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm, measuring the zeta potential of the composition comprising the colloids, and selecting composition having a zeta potential of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting an activated vascular site. The claims require that the size of the colloids in the composition to be between about 10 nm to about 400 nm. Moreover, Applicants unexpectedly discovered that about +30

mV to +65 mV is the optimal range of zeta potential for targeting an agent to an activated vascular site (figures 2 and 3). Thus, the claims of the present invention also require measuring the zeta potential of the composition comprising the dispersed colloids and selecting compositions having a zeta potential of between about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for targeting an activated vascular site.

In contrast, Thierry only teaches methods of preparing cationic liposomal compositions, wherein the diameter of the liposomes are between 200 nm to 3 μ m. This range of diameter is much broader than what is claimed by the present invention and only overlaps with the range claimed by the present invention from about 200 nm to about 400 nm. Moreover, the overlap in the two ranges is less than 10% of the range disclosed by Thierry. Additionally, Thierry does not teach methods of preparing compositions for enhanced efficacy of targeting an activated vascular site. The methods of Thierry does not include measuring the zeta potential of the composition and selecting composition having a zeta potential in the range of about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 for effective targeting to an activated vascular site. Thierry does not even disclose the zeta potential of the composition.

As discussed above, when an agent is mixed with a cationic lipid to form a composition, the composition can have various zeta potentials depending on the zeta potential of the agent and cationic lipid to begin with, the amount of each component in the composition, and the solution in which the components are formed. Accordingly, Thierry does not include all the steps recited by the claimed method, and the compositions prepared by the method of Thierry do not have the specific range of zeta potential recited in the claims.

Also, as discussed above, in *Atofina*, the court held that an earlier genus reference does not anticipate a narrow species, if the prior art reference does not describe the narrower claimed range with sufficient specificity. Like the fact situation in *Atofina*, Thierry does not disclose a method of obtaining liposomal compositions having the recited particle size and zeta potential with sufficient specificity. Thierry discloses obtaining a composition having particles with a diameter in the range of 200 nm to 3 μ m which is much broader than between about 10 nm to about 400 nm, the size of the particles recited in the claims. Also, Thierry does not disclose optimizing the zeta potential of the liposomal composition to between about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5. Thus, Thierry does not teach the range of the

particle size or zeta potential recited in the claims with sufficient specificity to anticipate the claims. Accordingly, Thierry does not teach or anticipate the claimed invention.

Obviousness of the claims in view of Unger or Thierry

Applicants respectfully point out that neither Unger nor Thierry would render claims 75, 76 and 78-81 obvious because neither of these references discloses or suggests the steps of measuring the zeta potential of the composition comprising the colloids and selecting composition having the recited range of zeta potential (between about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5) for targeting an activated vascular site. Moreover, the cited references do not disclose or suggest compositions having the recited particle size (about 10 nm to about 400 nm). Accordingly, the cited references do not provide motivation to modify the teachings of the references to include the steps of dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm, measuring zeta potential of the composition comprising the colloids, and selecting composition having the optimal range of zeta potential for targeting an activated vascular site as recited by the claims.

In general, the discovery of an optimum value in a known process is an obvious process. However, in *In re Antonie*, the court held that when the parameter optimized is not recognized to be a result-effective variable, optimization of that parameter is not an obvious step. *In re Antonie*, 195 USPQ 6 (CCPA 1977). Further, in *In re Soni*, the court held that Applicant's showing of substantial improved results for an invention and Applicant's statement that the results are unexpected are sufficient to establish unexpected results to overcome obviousness. *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995). Prior to Applicants' discovery, it was not known that optimizing zeta potential would improve the efficacy of an agent in targeting an activated vascular site. Applicants unexpectedly discovered that the optimal range of zeta potential for targeting an activated vascular site is between about +30 mV to +65 mV in about 0.05 mM KCl solution at about pH 7.5 (figures 2 and 3).

Accordingly, Unger and Thierry also do not render the claimed invention obvious.

Rejection Under 35 U.S.C. 103(a)

A. Claim 60 was rejected under 35 U.S.C. 103(a) as being unpatentable over Thierry or Unger.

Claim 60 has been amended to exclude liposomes. In contrast to the claimed invention, Thierry and Unger disclose liposomal preparations. Thus, neither Thierry nor Unger anticipates the claimed invention.

Claim 77 is directed to a method of modifying an agent to enhance its efficacy of targeting an activated vascular site comprising associating the agent with one or more cationic components to produce a composition having an optimal range, dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm, measuring the isoelectric point of the composition comprising the colloids, and selecting composition having an isoelectric point above 7.5 for targeting an activated vascular site. Applicants unexpectedly discovered that an isoelectric point above 7.5 improves targeting to activated vascular site.

As discussed above, neither Unger nor Thierry is directed to a method of modifying an agent to enhance its efficacy of targeting an activated vascular site. Moreover, neither Thierry nor Unger discloses nor suggests dispersing the composition in a medium to form colloids having a size of about 10 nm to about 400 nm, measuring the zeta potential of their composition, and selecting composition having an isoelectric point above 7.5. Thus, there is no motivation to modify the method of Unger or Thierry to include the steps of measuring the isoelectric point of the composition and selecting composition having an isoelectric point above 7.5 so that it has enhanced efficacy for specific targeting to activated vascular site. Accordingly, neither Unger nor Thierry renders the claimed invention obvious.

Applicants respectfully submit that when an agent is combined with a cationic component to form a composition, the composition does not necessarily have an isoelectric point above 7 because the agent may have a low isoelectric point to begin with. Nevertheless, the claim requires that the isoelectric point of the composition be above 7.5. Neither Unger nor Thierry discloses or suggests obtaining compositions having an isoelectric point above 7.5.

Accordingly, neither Unger nor Thierry renders the claimed invention obvious.

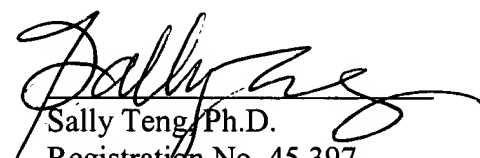
Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, they are invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

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